Use of slow-release melatonin in treatment-resistant depression

E. Jane Dalton, BSc; Debra Rotondi, BSc; Robert D. Levitan, MD; Sidney H. Kennedy, MD; Gregory M. Brown, MD, PhD

Dalton, Rotondi — Research Assistant, Depression Clinic, Centre for Addiction and Mental Health (CAMH-Clarke), Toronto, Ont.; Levitan — Research Head, Depression Clinic, CAMH, and Department of Psychiatry, University of Toronto; Kennedy — Clinical Director, Mood & Anxiety Disorders Program, CAMH, Department of Psychiatry, University of Toronto; Brown — Head, Neuroendocrinology Research Section, CAMH, and Department of Psychiatry, University of Toronto

Objective: To examine antidepressant augmentation with and hypnotic effects of slow-release melatonin (SR-melatonin) in patients with treatment-resistant depression. **Design:** Open-label trial. **Setting:** Tertiary care outpatient depression clinic. **Patients:** Nine outpatients who had failed to respond to 2 or more 8-week trials of antidepressant medication. **Interventions:** Patients received SR-melatonin 5 mg per day for the first 2 weeks and 10 mg per day for the final 2 weeks, in addition to their antidepressant medication. **Outcome measures:** Structured Clinical Interview for DSM-IV, Axis I Disorders, Hamilton Rating Scale for Depression (HRSD), Beck Depression Inventory, Response Style Questionnaire, sleep and fatigue measures. **Results:** One patient was excluded after 1 week because of the development of a mixed affective state. In the remaining 8 patients there was a 20% mean decrease in HRSD scores after 4 weeks of treatment, with no individual achieving an improvement of 50% or more. There was a 36% decrease on the 3-item HRSD related to insomnia, with 4 of 8 patients showing at least a 50% improvement on this measure. The greatest decrease in insomnia occurred during the last 2 weeks of the study, following the increase in dosage to 10 mg per day of SR-melatonin. Patients also reported significantly lower levels of fatigue post-treatment. **Conclusions:** SR-melatonin may be a useful adjunct for sleep, but does not substantially augment existing antidepressant therapies in some patients with treatment-resistant depression.

Objectif : Étudier l'effet de l'ajout au traitement antidépresseur de la mélatonine à libération prolongée (mélatonine LP) et ses effets hypnotiques chez les patients aux prises avec une dépression réfractaire. **Conception :** Essai ouvert. **Contexte :** Clinique de traitement tertiaire de la dépression en service externe. **Patients :** Neuf patients en service externe qui n'avaient pas réagi à deux essais ou plus de traitement aux antidépresseurs d'une durée de huit semaines. **Interventions :** Les patients ont reçu de la mélatonine LP à raison de 5 mg par jour pendant les deux premières semaines et de 10 mg par jour pendant les deux dernières semaines, en sus de leur médicament antidépresseur. **Mesures de résultats :** Entrevue clinique structurée pour DSM-IV, troubles de l'axe I, échelle de dépression de Hamilton (HRSD), inventaire de la dépression de Beck, questionnaire à réponses, mesures du sommeil et de la fatigue. **Résultats :**

Correspondence to: Robert D. Levitan, Centre for Addiction and Mental Health, 250 College St., Toronto ON M5T 1R8; fax 416 979-6821; Robert_Levitan@camh.net

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On a exclu un patient après une semaine à cause de l'apparition d'un état affectif mixte. Chez les huit patients restants, on a constaté une baisse moyenne de 20 % des résultats HRSD après quatre semaines de traitement, et aucun sujet n'a montré une amélioration de 50 % ou plus. On a constaté une diminution de 36 % des résultats des trois questions de l'échelle HRSD qui ont trait à l'insomnie, et quatre des huit patients ont montré une amélioration d'au moins 50 % de cette mesure. La réduction la plus marquée de l'insomnie s'est produite au cours des deux dernières semaines de l'étude après une augmentation de la dose à 10 mg par jour de mélatonine LP. Les patients ont aussi signalé des niveaux de fatigue beaucoup moins élevés après le traitement. **Conclusions :** La mélatonine LP peut être un traitement d'appoint utile pour faciliter le sommeil, mais elle n'améliore pas de façon substantielle l'effet du traitement antidépresseur déjà administré à certains patients aux prises avec une dépression réfractaire.

Introduction

Melatonin, a hormone secreted by the pineal gland primarily at night, plays an intrinsic role in the regulation of the sleep–wake cycle. Exogenous melatonin has been shown to exert synchronizing effects on circadian rhythms, phase-advancing the sleep of patients suffering from a delayed sleep-phase syndrome,[1,2] facilitating adaptation to jet lag[3,4] and synchronizing the sleep–wake cycles of blind patients to environmental light/dark cycles.[5,6] The hypnotic effects of melatonin have been widely reported in various populations.[7,8] For example, one study demonstrated that administration of 75 mg of melatonin over 14 days significantly increased the subjective assessment of total sleep time in patients with chronic insomnia.[9] In a recent review, it was reported that a 5-mg dose of melatonin administered over 4 weeks normalized the sleep pattern of patients with delayed sleep-phase syndrome.[10] Similarly, it has been reported that a single 80-mg dose of melatonin accelerated sleep initiation and sleep efficiency in normal subjects.[8,10] Furthermore, in elderly patients with insomnia, a 2-mg dose of slow-release melatonin (SR-melatonin) administered over a 3-week period normalized sleep patterns and improved sleep maintenance.[11,12]

A relation between biological rhythms, insomnia and melatonin points to a pathophysiologic role for melatonin in mood disorders. Consistent with this hypothesis, numerous studies have reported a decrease in nocturnal melatonin levels in patients with major depression[13,14] and in patients with disorders in which there is comorbid depression.[15] To our knowledge, only a single study has examined the possible therapeutic effects of exogenous SR-melatonin in patients with major depressive disorder.[16] In this study, patients were administered 5 to 10 mg of melatonin in combination with fluoxetine over a 4-week period. On average, patients reported a 50% increase in subjective sleep quality, although SR-melatonin had no effect on the rate of improvement of symptoms of major depressive disorder. There have, however, been no studies conducted in patients with treatment-resistant depression.

Many patients who fail to respond to standard antidepressant medications report significant insomnia, establishing a rationale for a sleep-targeted strategy in these patients. The goal of the current pilot study was to examine the hypnotic and antidepressant-augmenting effects of SR-melatonin in a group of patients with treatment-resistant depression. SR-melatonin has no demonstrated antidepressant efficacy as a monotherapy.[16] A slow-release formulation was used because it more closely simulates the endogenous nocturnal profile of melatonin than does immediate-release melatonin.[11,12]

Methods

Ethics approval for this study was obtained through the human subjects review committee at the University of Toronto. Nine patients with treatment-resistant depression were included in this study; all patients gave written informed consent. Patients were 22 to 73 years of age and were recruited from the outpatient clinic at the Centre for Addiction and Mental Health — Clarke Division. All patients were diagnosed with major depressive disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV), using the Structured Clinical Interview for DSM-IV, Axis I Disorders (SCID).[17] Patients were required to score 18 or greater on the 17-item Hamilton Rating Scale for Depression (HRSD).[18] All patients also met the criteria for treatment-resistant depression, which was defined as the failure to respond to 2 or more trials of antidepressant medication from different drug classes, each at adequate therapeutic doses, for at least 8 weeks.

Exclusion criteria included bipolar disorder, eating disorders, primary sleep disorders, major medical illnesses, endocrine disorders, psychotic symptoms, active alcohol or substance abuse and active suicidal ideation.

At the time of recruitment, all patients had been receiving treatment with an antidepressant medication for at least 8 weeks, but continued to meet criteria for major depression. Patients continued taking the antidepressant medication, at the same dosage, throughout the study. At the first visit, patients received SR-melatonin in 5-mg capsules and were instructed to take this half an hour before bedtime. The daily dose was increased to 10 mg if the patient's HRSD score had not decreased by 50% at Week 2. Patients were assessed at baseline using the SCID, the HRSD, the Beck Depression Inventory (BDI),[19] and the Response Style Questionnaire (RSQ; unpublished scale). The RSQ is a self-report scale designed to measure response style to depression, which yields scores on 2 factors: distraction and rumination. All ratings were repeated after 2 and 4 weeks, except the RSQ, which was repeated only after Week 4.

Patients also completed daily ratings of sleep length, interruptions, naps and sleep quality. Sleep quality was assessed using a 7-item self-report fatigue scale and the Stanford Sleepiness Scale (SSS).[20] The 7-item fatigue scale measures present level of energy, and the SSS measures present level of sleepiness. Weekly averages for each of the 2 sleep scales, sleep length, naps and interruptions, were calculated using pro-rated values for missing days.

Changes in clinical measures of mood and sleep were assessed using a repeated measures ANOVA. Post hoc comparisons were performed using paired *t*-tests, applying the Bonferroni correction procedure for multiple *t*-tests. The SSS and the fatigue scale, which are narrowly scored categorical variables, were analyzed using nonparametric statistics (Friedman 2-way ANOVA).

Results

Of the 9 patients, 1 was excluded after 1 week because of the development of a mixed affective state, characterized by ongoing depression, agitation, and decreased need for sleep. By the end of Week 2, none of the patients showed a 50% decrease on the HRSD; therefore, the dosage of SR-melatonin was increased for all patients to 10 mg per day for the final 2 weeks of the study. Table 1 summarizes demographics, antidepressant regimens, and HRSD scores before and after treatment for each of the 8 patients who completed the study. Table 2 summarizes the mean depression scores over the 4 weeks of study for the 8 patients.

The HRSD scores were found to drop significantly over time; however, none of the patients had a score below 10 at Week 4, and the mean improvement in these scores was modest at 20% (standard deviation [SD] 13.9%; range 0% to 45%). None of the patients showed a 50% improvement at Week 4. The ruminative scale of the RSQ also showed a significant decline over time from baseline to Week 4, with the percentage change scores indicating a modest mean improvement of 16% (SD 18.2%; range 3% to 47%).

With respect to sleep variables, the 3 insomnia items (early, middle and late) from the HRSD (i.e., "HRSD-3") were extracted to examine the effects of treatment on sleep alone (Tables 1 and 2). Insomnia was found to decrease significantly over time in all subjects. Applying a Bonferroni correction procedure, a significant difference

Table 1: Patient demographics and treatment regimen in the 8 patients with treatment-resistant depression

						HRSD		HRSD-3¶	
Sex*	Age, yr	Current diagnosis(es)	Current antidepressant§	Dosage, mg/d	Duration of current episode, yr	Week 0	Week 4 (% change)	Week 0	Week 4 (% change)
M	51	MDD†	Venlafaxine	225	13	23	23 (0)	6	3 (50)
M	39	MDD, social phobia	Fluoxetine	60	6	21	18 (6)	4	3 (25)
M	22	MDD	Moclobemide	450	5	21	16 (24)	5	1 (80)
F	49	MDD, panic disorder‡	Venlafaxine	375	2	27	19 (30)	6	3 (50)
F	73	MDD	Nortripyline	75	1	18	14 (22)	4	2 (50)
F	42	MDD, panic disorder	Fluoxetine	40	4	22	20 (10)	6	4 (33)
F	53	MDD	Paroxetine	30	2	24	21 (13)	2	2 (0)
F	50	MDD	Sertraline	150	1	20	11 (45)	3	3 (0)

*M = male; F = female
†MDD = major depressive disorder
‡Panic disorder (without agoraphobia)
§Drug regimen followed for a minimum of 8 weeks before entering study
¶HRSD-3: includes 3 insomnia items only

was found between baseline and Week 4. Percentage change scores indicated a mean improvement of 36% (SD 27.4%). Four of the 8 subjects experienced a 50% or greater improvement on this measure at Week 4.

Scores on the fatigue scale were also significantly lower post-treatment (χ^2 7.62, df 3, $p = 0.05$). No significant effects over time were observed for the other sleep measures.

Discussion

In a small group of patients with treatment-resistant depression, we found that a 5- to 10-mg per day dosage of SR-melatonin decreased insomnia (in 6 of 8 patients), but had a minimal effect on mood, overall. The improvement in sleep appeared to be greatest following the increase in dosage to 10 mg per day (i.e., between Week 2 and Week 4).

Considering the morbidity associated with refractory depression, the effect of SR-melatonin on insomnia may be clinically relevant. Consistent with this, a previous study demonstrated that SR-melatonin had an effect on subjective sleep quality, but not on mood, in patients with uncomplicated depression.[16] The similar pattern of the current findings with the previous study supports the sleep-inducing qualities of SR-melatonin in depressed populations, and suggests that SR-melatonin may be of some benefit in both uncomplicated and treatment-resistant depression.

Other than the excluded patient who developed a mixed affective state, no significant side effects were noted in the patients over the course of the study. One patient did report a mild increase in somnolence, and another reported a small increase in agitation at the higher dose of SR-melatonin. The general lack of side effects is consistent with the previous study in patients with uncomplicated depression.[16]

The patient who developed a mixed affective state was a 24-year-old woman with no history of hypomania; she was not aware of any family history of bipolar illness. Although the mechanism of her mixed state is unknown, a previous case report describes an association between melatonin levels and affective switches in a drug-free patient with bipolar disorder.[21]

In summary, although the open-label design and small sample size of this pilot study limit interpretation of the findings, it appears that SR-melatonin may be a useful adjunct for sleep, but does not substantially augment existing antidepressant therapies in treatment-resistant depression.

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Table 2: Measures of depressive symptoms at Weeks 0, 2 and 4 of treatment with SR-melatonin in 8 patients with treatment-resistant depression

	Mean scores (standard deviation)			Time effect‡			
Scale	Week 0	Week 2	Week 4	*F*	df	*p*	Post-hoc comparisons§
BDI	38.1 (10.5)	35.4 (8.6)	34.0 (5.4)	1.74	2,5	0.26	
HRSD	22.0 (2.4)	18.6 (3.1)	17.8 (3.9)	22.99	2,6	0.002§	Weeks 0 & 2: $t = 4.22$; df = 7; $p = 0.004$¶ Weeks 0 & 4: $t = 3.99$; df = 7; $p = 0.005$¶
HRSD-3*	4.5 (1.5)	3.9 (1.5)	2.6 (0.9)	21.62	2,6	0.002§	Weeks 0 & 4: $t = 3.64$; df = 7; $p = 0.008$¶ Weeks 2 & 4: $t = 2.76$; df = 7; $p = 0.028$**
HRSD-14†	17.5 (2.7)	15.0 (2.9)	15.1 (3.8)	4.38	2,6	0.007	Weeks 0 & 2: $t = 2.96$; df = 7; $p = 0.02$**
RSQ-distraction	16.1 (4.6)	—	14.0 (4.0)	2.91	1,7	0.13	
RSQ-rumination	53.6 (9.8)	—	44.6 (12.0)	5.85	1,7	0.05¶	

*HRSD-3: includes 3 insomnia items only
†HRSD-14: excludes 3 insomnia items
‡Week 0 compared with Week 4 using repeated-measures ANOVA
§Significance level set at $p < 0.01$ using the Bonferroni Correction Procedure
¶$p < 0.01$
**$p < 0.05$

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